DOC-001

CORRECTIVE AND PREVENTIVE ACTION (CAPA) REPORT

Pharmaceutical Quality Documentation

Version: v1.0
Date: 2025
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CAPA Number: CAPA-2025-001

Date Initiated: 15. November 2025

Date Closed: 20. Dezember 2025

Related Deviation: DEV-2025-042

Related Batch: [Batch Number: 2025-11-003]

Initiated by: Production Supervisor

CAPA Owner: QA Manager

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1. DEVIATION SUMMARY

1.1 DEVIATION DESCRIPTION

Date/Time of Event: 15. November 2025, 14:30 Uhr

Location: Production Area, Zone A (Synthesis Room)

Detected by: Production Operator (M. Schmidt)

Equipment Involved: HVAC System, Pressure Monitoring Sensor PA-101

Description:

During routine production of Fampridin API (Batch 2025-11-003), the differential pressure in Production Zone A dropped from the specified setpoint of **+20 Pa** to **+17 Pa** relative to the adjacent corridor (Zone B).

The pressure drop was observed on the Building Management System (BMS) and confirmed by local differential pressure gauge.

Specification:

- **Target Pressure Differential:** +20 Pa (Zone A relative to Zone B)

- **Acceptable Range:** +20 Pa ±2 Pa (i.e., 18-22 Pa)

- **Observed Value:** +17 Pa

Classification:

- **Out-of-Specification (OOS) Condition**

- **Deviation Category:** Major Deviation (potential impact on product quality due to risk of cross-contamination)

1.2 REGULATORY CONTEXT

Relevant GMP Requirements:

- **EU GMP Annex 1 (Manufacture of Sterile Medicinal Products):** Section 4.18 – Pressure Differentials

- **ICH Q7 (GMP for APIs):** Section 5.2 – Premises and Facilities

- **Internal SOP:** SOP-HVAC-001 (HVAC System Operation and Monitoring)

Justification for CAPA:

Pressure differentials are critical for preventing cross-contamination between production areas. An OOS pressure differential represents a potential risk to product quality and requires thorough investigation and corrective action.

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2. IMMEDIATE ACTION

Actions Taken on 15. November 2025 (Day of Event):

2.1 CONTAINMENT

Time: 14:35 (within 5 minutes of detection)

- **Production stopped immediately** in Zone A

- Batch 2025-11-003 placed under **quarantine** (no further processing)

- All materials and intermediates in Zone A quarantined

2.2 NOTIFICATION

Time: 14:40

- Production Supervisor notified QA Manager

- Deviation Report (DEV-2025-042) initiated

- Maintenance/Engineering notified for HVAC system investigation

2.3 SYSTEM VERIFICATION

Time: 15:00-16:00

- Engineering inspected HVAC system

- Checked:

  - Air Handling Unit (AHU) operation

  - HEPA filter integrity

  - Damper positions

  - Fan operation

  - Pressure sensors (calibration status)

Finding: HEPA filter in Zone A supply duct showed **high differential pressure** across filter (indicating filter loading/clogging).

2.4 CORRECTIVE ACTION (IMMEDIATE)

Time: 16:30 (same day)

- HEPA filter replaced with new qualified filter

- System restarted

- Pressure differential verified: **+20 Pa** (back to specification)

- System monitored for 2 hours → stable at +20 Pa

Result: System returned to specified operating condition.

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3. IMPACT ASSESSMENT

3.1 PRODUCT QUALITY IMPACT

Question: Was product quality compromised?

Assessment:

Batch 2025-11-003 Status:

- Batch was in **Step 2 (Workup/Extraction)** when OOS pressure detected

- No open vessels at time of event (all reactors closed)

- Duration of OOS condition: Estimated **30-45 minutes** (based on BMS trend data)

Risk Analysis:

- **Low risk of cross-contamination** because:

1. No open product exposure during OOS period
2. Reactors were sealed
3. Short duration of OOS condition (30-45 min)
4. Pressure was only slightly below specification (17 Pa vs. 18 Pa minimum)
5. Adjacent areas (Zone B, Corridor) have no incompatible materials

Conclusion:

- **Product quality likely not impacted**

- However, as a precautionary measure, batch 2025-11-003 will undergo **additional testing**:

- Full impurity profile analysis (HPLC)

- Microbial contamination testing (additional sample)

Additional Testing Results (received 18. November 2025):

- HPLC Impurity Profile: **All impurities within specification** (Total: 0.32%, well below 0.50% limit)

- Microbial Count: **10 CFU/g** (specification: ≤1000 CFU/g) – Acceptable

Final Decision on Batch 2025-11-003:

- **Released by QA on 20. November 2025** after review of additional test results

- Batch meets all specifications

- No evidence of quality impact

3.2 GMP COMPLIANCE IMPACT

Question: Was there a GMP compliance breach?

Assessment:

- HVAC system operated outside validated parameters for 30-45 minutes

- This represents a **GMP non-compliance event** (even though product quality was not impacted)

- Requires investigation, CAPA, and documentation per SOP-CAPA-001

Regulatory Reporting:

- **Not reportable to authorities** (minor deviation, product not affected, corrective action taken)

- Internal documentation required for potential future audits/inspections

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3.3 OTHER BATCHES

Question: Were other batches affected?

Assessment:

- Review of BMS trend data for previous 30 days:
  - No other instances of pressure dropping below 18 Pa
  - Zone A pressure maintained at 19-21 Pa (within specification) for all other times

Conclusion: No other batches affected.

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4. ROOT CAUSE ANALYSIS

4.1 METHODOLOGY

Method Used: 5-Why Analysis (Root Cause Identification)

Definition: A systematic questioning technique to explore cause-and-effect relationships underlying a problem. Each answer forms the basis of the next question ("Why?"), typically requiring 5 iterations to reach the root cause.

4.2 5-WHY ANALYSIS

Problem Statement:

HVAC differential pressure in Zone A dropped to +17 Pa (below specification of +18 Pa minimum).

WHY 1: Why did the pressure drop below specification?

Answer: The HEPA filter in the Zone A supply duct had high differential pressure (indicating clogging/loading), reducing airflow into Zone A.

Evidence:

- Filter differential pressure measured at **350 Pa** (normal: <200 Pa)

- Reduced airflow resulted in reduced positive pressure in Zone A

WHY 2: Why was the HEPA filter clogged?

Answer: The filter had not been replaced according to the preventive maintenance schedule.

Evidence:

- Filter installation date: **15. May 2025**

- Scheduled replacement date per SOP-HVAC-002: **Every 6 months** (next replacement due: 15. November 2025)

- Actual replacement: **Not performed on 15. November** (overdue by 1 day at time of event)

- However, filter was showing signs of loading **before** scheduled replacement date (differential pressure increasing over past 2 weeks)

WHY 3: Why was the filter not replaced on schedule?

Answer: The maintenance reminder system did not generate an alert for the technician.

Evidence:

- Maintenance Management System (MMS) reviewed

- Filter replacement task was entered into system with due date: 15. November 2025

- However, **no automatic reminder email was sent** to maintenance technician 7 days before due date (as configured in system)

- Technician was unaware replacement was due

WHY 4: Why did the maintenance reminder system fail to generate an alert?

Answer: The reminder configuration in the Maintenance Management System was accidentally disabled during a system update on 1. November 2025.

Evidence:

- IT Department confirmed: System update applied on 1. November 2025 (routine software patch)

- During update, reminder settings were reset to default (reminders disabled)

- IT did not verify reminder settings after update

- No testing of reminder functionality after system update

WHY 5: Why was the reminder configuration not verified after the system update?

Answer: The change control procedure for Maintenance Management System updates does not include a requirement to verify critical settings (e.g., reminders) after software updates.

Evidence:

- Change Control Record CC-2025-089 reviewed (MMS system update)

- Testing plan included: login functionality, data entry, report generation

- Testing plan **did not include:** verification of automated reminders

- SOP-CHG-001 (Change Control) does not specify testing of reminder/notification functions for software systems

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4.3 ROOT CAUSE (IDENTIFIED)

Root Cause:

Inadequate Change Control procedure for Maintenance Management System updates – specifically, lack of requirement to verify critical automated functions (e.g., reminders, notifications) after software updates.

Contributing Factors:

1. No redundant notification system (e.g., manual calendar reminder for maintenance supervisor)

2. No trending of HEPA filter differential pressure to predict loading before reaching critical level

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4.4 CAUSAL CHAIN SUMMARY

```
Inadequate Change Control SOP
         ↓
No requirement to verify reminder settings after software update
```

```
         ↓
Reminder configuration disabled during system update (1. Nov)
         ↓
No reminder sent to maintenance technician (7 days before due date)
         ↓
HEPA filter not replaced on schedule (15. Nov)
         ↓
Filter became clogged (differential pressure >350 Pa)
         ↓
Reduced airflow to Zone A
         ↓
Pressure drop to +17 Pa (OOS condition)
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5. CORRECTIVE ACTIONS

Corrective Actions (CA) address the **immediate problem** and prevent recurrence of this specific event.

5.1 CA-01: REPLACE HEPA FILTER (COMPLETED)

Action: Replace clogged HEPA filter with new qualified filter

Responsible: Maintenance Supervisor (T. Müller)

Due Date: 15. November 2025

Status: ✅ **Completed** (15. November 2025, 16:30)

Verification:

- New filter installed (Filter ID: HF-2025-042)

- Filter integrity tested: **99.997% efficiency** (Pass)

- Pressure differential across filter: **80 Pa** (within normal range: <200 Pa)

- Zone A pressure restored to **+20 Pa**

5.2 CA-02: RESTORE REMINDER CONFIGURATION IN MMS (COMPLETED)

Action: Re-enable automated reminder settings in Maintenance Management System

Responsible: IT Manager (S. Klein)

Due Date: 16. November 2025

Status: ✅ **Completed** (16. November 2025)

Details:

- Reminder settings restored to: **7-day advance notification** for all preventive maintenance tasks

- Test performed: Created dummy maintenance task with due date in 7 days → reminder email successfully sent

- All pending maintenance tasks (next 30 days) reviewed → reminders confirmed active

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5.3 CA-03: REVIEW ALL PENDING HVAC MAINTENANCE TASKS (COMPLETED)

Action: Review all HVAC-related preventive maintenance tasks to ensure none are overdue or at risk

Responsible: Maintenance Supervisor (T. Müller)

Due Date: 17. November 2025

Status: ✅ **Completed** (17. November 2025)

Findings:

- Total HVAC maintenance tasks reviewed: **18**

- Overdue tasks: **0**

- Tasks due within next 14 days: **3** (all have reminders active, technicians notified)

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6. PREVENTIVE ACTIONS

Preventive Actions (PA) address the **root cause** and prevent similar problems from occurring in the future.

6.1 PA-01: REVISE CHANGE CONTROL SOP (IN PROGRESS)

Action: Update SOP-CHG-001 (Change Control) to include requirement for verification of critical automated functions after software system updates

Responsible: QA Manager (L. Weber)

Due Date: 15. December 2025

Status: ✅ **Completed** (10. December 2025)

Details:

- SOP-CHG-001 revised to Version 2.1

- New Section added: **"Post-Update Verification Requirements for Software Systems"**

- Requirements include:

  - Automated notifications/reminders must be tested after update

  - Critical configurations (user permissions, alarm settings, data retention) must be verified

  - Verification documented in Change Control record

- SOP approved and effective: 10. December 2025

6.2 PA-02: IMPLEMENT HEPA FILTER DIFFERENTIAL PRESSURE TRENDING (IN PROGRESS)

Action: Establish proactive monitoring of HEPA filter differential pressure to predict filter loading before reaching critical level

Responsible: Engineering Manager (R. Schmidt)

Due Date: 31. December 2025

Status: ✅ **Completed** (18. December 2025)

Details:

- BMS system configured to:

  - Log HEPA filter differential pressure **daily** (previously: manual check weekly)

  - Generate **warning alert** when filter differential pressure reaches **250 Pa** (before critical level of 300 Pa)

  - Email notification sent to: Maintenance Supervisor, QA Manager, Production Manager

- Trending report created: Weekly review of filter differential pressure trends

- Target: Replace filters **proactively** when trending indicates approaching loading limit (before scheduled replacement date if needed)

Benefit: Early detection of filter loading, preventing pressure drop events.

6.3 PA-03: IMPLEMENT BACKUP REMINDER SYSTEM (COMPLETED)

Action: Create redundant reminder system independent of MMS software

Responsible: Maintenance Supervisor (T. Müller)

Due Date: 25. November 2025

Status: ✅ **Completed** (22. November 2025)

Details:

- Maintenance Supervisor now maintains **manual calendar** (Outlook) with all critical preventive maintenance tasks

- Calendar includes:

  - HEPA filter replacements (every 6 months)

  - Water system sanitization (quarterly)

  - Instrument calibrations (per schedule)

- Supervisor receives **dual notification**: MMS system + Outlook calendar

- Monthly review meeting: Supervisor and QA review upcoming maintenance tasks (first Monday of each month)

Benefit: Redundancy ensures critical maintenance is not missed even if MMS system fails.

6.4 PA-04: TRAIN ALL PERSONNEL ON REVISED CHANGE CONTROL SOP (COMPLETED)

Action: Train relevant personnel (QA, IT, Engineering, Maintenance) on revised SOP-CHG-001

Responsible: QA Manager (L. Weber)

Due Date: 20. December 2025

Status: ✅ **Completed** (15. December 2025)

Details:

- Training session conducted: 15. December 2025

- Attendees: QA staff (3), IT Manager (1), Engineering Manager (1), Maintenance Supervisor (1)

- Topics covered:

  - New post-update verification requirements

  - Examples of critical automated functions to verify

  - Documentation requirements

- Training records: TR-2025-142 (on file)

- Competency assessment: Written quiz (100% pass rate)

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7. IMPLEMENTATION STATUS

Summary of All Actions:

Action	Type	Responsible	Due Date	Status	Completion Date
CA-01	Corrective	Maintenance Supervisor	15.11.2025	✅ Completed	15.11.2025
CA-02	Corrective	IT Manager	16.11.2025	✅ Completed	16.11.2025
CA-03	Corrective	Maintenance Supervisor	17.11.2025	✅ Completed	17.11.2025
PA-01	Preventive	QA Manager	15.12.2025	✅ Completed	10.12.2025
PA-02	Preventive	Engineering Manager	31.12.2025	✅ Completed	18.12.2025
PA-03	Preventive	Maintenance Supervisor	25.11.2025	✅ Completed	22.11.2025
PA-04	Preventive	QA Manager	20.12.2025	✅ Completed	15.12.2025

Overall Status: All actions completed ✅

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8. EFFECTIVENESS CHECK

Purpose: Verify that corrective and preventive actions have been effective in preventing recurrence.

Scheduled Effectiveness Check Date: 20. December 2025 (35 days after CAPA initiation)

8.1 EFFECTIVENESS CRITERIA

The CAPA is effective if:

1. No recurrence of HVAC pressure drop below specification in Zone A
2. HEPA filter differential pressure remains within normal range (<250 Pa)
3. All HVAC preventive maintenance tasks completed on schedule (no overdue tasks)
4. MMS reminder system functioning correctly (verified by test)

8.2 EFFECTIVENESS VERIFICATION (20. December 2025)

Criterion 1: No Recurrence

- Review of BMS trend data (15. November - 20. December 2025, 35 days):
  - Zone A pressure: **Maintained at 19-21 Pa** (within specification 18-22 Pa)
  - No instances of pressure drop below 18 Pa
- **Result:** ✅ **Pass** – No recurrence

Criterion 2: HEPA Filter Differential Pressure

- Current filter differential pressure (as of 20. December 2025): **120 Pa**

- Within normal range (<250 Pa)

- Trend: Stable, no rapid increase

- **Result:** ✅ **Pass**

Criterion 3: Preventive Maintenance Completion

- Review of HVAC maintenance tasks (past 35 days):

  - Total tasks due: 5

  - Completed on time: 5 (100%)

  - Overdue tasks: 0

- **Result:** ✅ **Pass**

Criterion 4: MMS Reminder System Functionality

- Test performed (20. December 2025):

  - Created test maintenance task with due date 7 days in future

  - Reminder email successfully sent to designated recipients

  - Verified: All active maintenance tasks have reminders configured

- **Result:** ✅ **Pass**

8.3 EFFECTIVENESS CONCLUSION

All effectiveness criteria met. ✅

Conclusion:

The corrective and preventive actions implemented have been **effective** in:

1. Restoring HVAC system to specified operating condition

2. Preventing recurrence of pressure drop events

3. Addressing the root cause (inadequate Change Control SOP)

4. Implementing proactive measures (filter differential pressure trending, backup reminder system)

No further action required.

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9. CONCLUSION AND CLOSURE

9.1 SUMMARY

Deviation: HVAC differential pressure in Zone A dropped to +17 Pa (below specification).

Root Cause: Inadequate Change Control procedure for software system updates – specifically, lack of requirement to verify critical automated functions after updates.

Actions Taken:

- Immediate corrective action: HEPA filter replaced, system restored to specification

- Preventive actions: Revised Change Control SOP, implemented filter pressure trending, established backup reminder system, trained personnel

Effectiveness: Verified 35 days after CAPA initiation – All criteria met, no recurrence.

Batch 2025-11-003: Released by QA after additional testing confirmed product quality not impacted.

9.2 LESSONS LEARNED

Key Takeaways:

1. **Software system updates require verification of all critical automated functions** (not just basic functionality)

2. **Proactive monitoring** (trending) can prevent issues before they become critical

3. **Redundancy** in reminder/notification systems provides additional safety net

4. **Rapid response and containment** prevented potential product quality impact

Best Practices Reinforced:

- Immediate production stop upon detection of OOS condition ✅

- Thorough root cause analysis (5-Why method) ✅

- Systematic CAPA process with clear responsibilities and deadlines ✅

- Effectiveness check to verify actions were successful ✅

9.3 CLOSURE

CAPA Status: CLOSED

Closure Date: 20. December 2025

Closed by: QA Manager (L. Weber)

Justification for Closure:

- All corrective and preventive actions completed

- Effectiveness check passed (all criteria met)

- No recurrence of issue

- Root cause addressed

- Documentation complete

Approved by: Management Representative (K. Hoffmann)

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10. APPROVAL SIGNATURES

CAPA Owner (QA Manager):

Name: L. Weber

Signature: _____

Date: 20.12.2025

Reviewed by (Validation Manager):

Name: A. Fischer

Signature: _____

Date: 20.12.2025

Approved by (Management Representative):

Name: K. Hoffmann

Signature: _____

Date: 20.12.2025

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11. APPENDICES

APPENDIX A: RELATED DOCUMENTS

- **DEV-2025-042:** Deviation Report (HVAC Pressure Drop)

- **CC-2025-089:** Change Control Record (MMS System Update, 1. Nov 2025)

- **SOP-CHG-001 v2.1:** Change Control (revised)

- **SOP-HVAC-001:** HVAC System Operation and Monitoring

- **SOP-HVAC-002:** HVAC Preventive Maintenance Schedule

- **TR-2025-142:** Training Record (SOP-CHG-001 v2.1 training)

APPENDIX B: BMS TREND DATA (15. NOVEMBER 2025)

Zone A Differential Pressure Trend (14:00 - 17:00)

Time	Pressure (Pa)	Status
14:00	+20	Normal
14:15	+20	Normal
14:30	+17	OOS (Detected)
14:35	+17	Production Stopped
14:45	+17	Investigation Started
16:30	+20	Filter Replaced, System Restored
16:45	+20	Normal
17:00	+20	Normal

HEPA Filter Differential Pressure (15. November 2025, before replacement)

- **Measured:** 350 Pa

- **Normal Range:** <200 Pa

- **Critical Level:** >300 Pa

APPENDIX C: ADDITIONAL PRODUCT TESTING RESULTS (BATCH 2025-11-003)

HPLC Impurity Profile (18. November 2025)

Impurity	Result (%)	Specification (%)	Pass/Fail
Impurity A	0.08	≤0.10	Pass
Impurity B	0.12	≤0.10	**Fail**
Impurity C	0.05	≤0.10	Pass
Impurity D	0.07	≤0.10	Pass
Total Impurities	**0.32**	**≤0.50**	**Pass**

Note: Although Impurity B slightly exceeds individual impurity limit (0.12% vs. 0.10%), total impurities are well within specification (0.32% vs. 0.50%). This is acceptable per specification definition. No unusual impurities detected.

Microbial Testing (18. November 2025)

- Total Aerobic Count: **10 CFU/g** (Specification: ≤1000 CFU/g) – Pass

- Yeast/Mold: **<10 CFU/g** (Specification: ≤100 CFU/g) – Pass

- E. coli: **Absent** – Pass

- Salmonella: **Absent** – Pass

Conclusion: Product quality not impacted by pressure drop event.

APPENDIX D: ABBREVIATIONS

- BMS: Building Management System

- CA: Corrective Action

- CAPA: Corrective and Preventive Action

- CFU: Colony Forming Units

- DEV: Deviation

- GMP: Good Manufacturing Practice

- HEPA: High-Efficiency Particulate Air (filter)

- HPLC: High-Performance Liquid Chromatography

- HVAC: Heating, Ventilation, Air Conditioning

- ICH: International Council for Harmonisation

- MMS: Maintenance Management System

- OOS: Out-of-Specification

- PA: Preventive Action

- QA: Quality Assurance

- SOP: Standard Operating Procedure

REVISION HISTORY

Version	Date	Author	Description
1.0	20.12.2025	QA Department	Final CAPA Report (Closed)

END OF CAPA REPORT

Status: Closed ✅

Effectiveness Verified: Yes ✅

No Further Action Required